An Analysis of the SmartCells Business Model and Its General Applicability Toward Building Successful Early-Stage Ventures in the Pharmaceutical Industry

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A Thesis in the Field of Biotechnology

for the Degree of Master of Liberal Arts in Extension Studies

Harvard University

May 2017

Abstract

SmartCells developed a technology that would re-engineer the existing pharmaceutical, insulin, to perform in a way that was safer and more efficacious than the original underlying drug (Zion, 2004). This novel approach to delivering insulin was in the late pre-clinical phase of development when the pharmaceutical giant, Merck & Co., acquired SmartCells and its technology in late-2010 (Carroll, 2010). The deal garnered national awareness for being one of the largest pre-clinical life-science deals in history (Booth, 2011). Even with this much attention, to date no one has critically analyzed the key factors nor the inner mechanics of SmartCells' unique ability to achieve such an outcome. This case study will delve into not only the critical external factors but also the internal events and decisions made by the company and its key management team members leading up to the Merck acquisition. Using publicly available technical papers, patents and published articles as well as interviews with former high-level SmartCells team members, this case study will determine the general applicability and potential for deploying the "SmartCells Business Model" to enhance the rate of success of early-stage pharmaceutical ventures.

Dedication

This effort is dedicated to my mother, father and grandmother who always believed in me and encouraged me to seek higher education, and to my fiancé, Danielle, whose consistent, unconditional support throughout this endeavor has given me the strength to complete this degree.

Acknowledgements

I would like to thank my research directors, Drs. Whitehead and Zion, for their support and guidance. Dr. Whitehead's technical knowledge and problem solving capabilities are truly inspiring; her leadership style has given me something to aspire to in my career. Her keen insights into this paper and focused questions molded this case study.

Without Dr. Zion's unrestricted access to SmartCells this case study would not have been possible. I thank him for answering all of my questions and discussing the many aspects of what made SmartCells such a success. Outside of this thesis, as a personal friend, he has been a great role model in my life and inspired me to be an engineer. For all of that, and more, I am truly grateful.

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Chapter 1

Introduction

On December 2, 2010, the Wall Street Journal announced that Merck and Co. had agreed to acquire a relatively unknown start-up pharmaceutical company, SmartCells, Inc., located in Beverly, Massachusetts, for over $500M in upfront and milestone payments (Rockoff, 2010). The acquisition amount, large by any standard, was impressive given that SmartCells had relied solely on a modest sum of angel investments and grant funds, never raised a dollar of institutional venture capital (VC) money and had yet to run a single clinical trial with its technology (McBride, 2010). Similar pre-clinical deals in the pharmaceutical industry between 2005 and 2012 that consisted of upfront and milestone payments tended to lie within the $400M and $600M range (Giniatullina, Boorsman, Mulder, & van Deventer, 2013). However, pre-clinical biotechnology deals between 2006 and 2010 had very low upfront amounts that were between $8M and $12M (Thau & Delcheva, 2012). According to at least one source, the upfront amount for the SmartCells acquisition exceeded $80M and interviews with former SmartCells team members indicate the upfront amount exceeded nine figures (Booth, 2011). Furthermore, most of the $400M and $600M range deals involved the acquisition of VC-backed companies that likely raised significantly more capital than SmartCells thereby diminishing the investment return value for these deals.

The upfront and total return on investment (ROI) put SmartCells at or near the top of the list of successful life-science angel investments and spawned phrases such as the "SmartCells model" for aspiring entrepreneurs to adopt in the wake of the SmartCells success (Booth, 2011). In modern day start-up ventures throughout the industry, the "SmartCells model" has become what is ubiquitously known as a capital efficient company, relying aggressively on non-dilutive financing and angel investors with nearly rigorous aversion to institutional and/or VC financing. Importantly, up until the time of the SmartCells acquisition, no pharmaceutical start-up company had demonstrated that one could build an asset that could not only survive but actually achieve a successful exit with so little financing from non-institutional, individual investors. Since then, entrepreneurs have paid much attention to the SmartCells' capital efficient model as a potential way to build companies, especially given the increasingly scarce sources of private capital available to nascent life-science ventures.

The focus of this case study, therefore, is to analyze the key elements that contributed to SmartCells' success and determine which elements can be generalized and which are specific to SmartCells' unique circumstances. These key success elements can be divided into two major categories: business planning and navigating the technical development. The two categories, however, are symbiotic and therefore not completely separable e.g. as technical issues arose, business decisions were made to support such paths and vice-versa. Technical issues include the specific risks associated with the composition of the underlying technology, manufacturing-related issues, and the safety and efficacy work required to mitigate those risks. These technical risks are coupled with financing and liquidity risks on the business side e.g. deciding which critical efforts

required the most support with limited resources and striking a balance between minimizing company expenditures while still making progress.

As may be expected from any high-technology start-up venture, the process from 2004-2010 was anything but linear. SmartCells was a life-science venture built from the ground up with a patent-pending technology, licensed to the company from the Massachusetts Institute of Technology (M.I.T.), with three co-founders who put together a plan with the help of early prospective investors to step down incremental risk and build value. With the perspective that value is an inverse function of risk, the founders decided that above all the key to success was a capital-efficient, lean operating model where each and every day was spent reducing risk (SmartCells, 2016). This may seem like an obvious approach to building successful ventures, but until that time there was a widely-held belief that the capital requirements for pharmaceutical ventures were so high that raising and deploying large amounts of funds from VC firms was absolutely necessary. Capital efficient, incremental risk reduction for biotech ventures seemed contrary to conventional wisdom.

At the heart of this analysis lies a central question: was SmartCells a once-in-a-lifetime outlier that benefited from a non-repeatable confluence of key elements, or can future enterprises generally apply the core elements of the SmartCells' strategy to improve their chances of success and increase shareholder returns?

Chapter II

Materials and Methods

This case study is based on publicly available reports, press-releases, technical disclosures, such as the doctoral thesis of Dr. Todd C. Zion (SmartCells co-founder), patents awarded to SmartCells, and interviews with industry veterans. Most notable and unique to this thesis are the personal interviews with SmartCells team members who provided their perspectives on the key business, technical, and human capital elements that contributed to SmartCells' success.

Chapter III

Results

SmartCells was co-founded on August 15, 2003 by Todd C. Zion, Ph.D., the Company's President and CEO, and Jackie Y. Ying, Ph.D., Dr. Zion's Ph.D. thesis advisor at M.I.T. where he developed the underlying technology that formed the basis for the company (Mervis, 2015). Dr. Zion also included several business school students as nominal co-founders in recognition of their helping Dr. Zion and SmartCells win the Robert P. Goldberg Grand Prize in the 2003 M.I.T. $50K Entrepreneurship Competition (Massachusetts Institute of Technology, 2003). Shortly after the company's founding, Dr. Zion recruited two key members of the SmartCells management team, Dr. Thomas Lancaster and Mr. James Herriman, who would become integral co-founders and management team members through the Merck acquisition (Matheson, 2013).

SmartInsulin was a technology that aimed to make an existing, proven pharmaceutical work more safely and effectively than the original formulation. However, as described in more detail in the Technical section, the enabling technical innovation required chemical modification of the underlying insulin molecule. The change in chemistry of the underlying drug necessitated a full Food and Drug Administration (FDA) New Drug Application (NDA) regulatory approval process, which

meant that SmartInsulin was on a minimum ten to fifteen year product development timeline with a total cost expected to exceed $1B (Van Norman, 2016). In addition, further innovation was required to address the known safety, efficacy and manufacturing risks of the technology licensed from M.I.T. before it could enter the regulatory process. Therefore, it was clear that at some point along the product development trajectory, SmartCells would need to partner with a well-capitalized and experienced pharmaceutical company to bring their product to market. The question at hand was which financing and operating model best addressed the capital and technical development risk profile.

Business

After winning the M.I.T. $50K Entrepreneurship Competition, SmartCells began to further develop their business model. The initial idea, as with most start-ups, was to raise large sums of money from VCs. However, this did not appear to be the best or the most desirable initial path for SmartCells (SmartCells, 2016). VCs in 2003-2004 had large amounts of capital but were moving away from high-risk, early-stage investments such as SmartCells, because they had overinvested during the "dot com" bubble and failed to see bright prospects for high valued initial public offerings (IPOs) (Pan, 2005). Furthermore, the VC investment thesis involved deploying tens of millions of dollars at the outset rather than the "modest dollars required for SmartCells to step down risk incrementally" (SmartCells, 2016). Put simply, most VCs wanted to invest large amounts of capital in less risky ventures but had no desire to invest comparatively smaller

amounts of capital to “de-risk” assets and make them more attractive for future investment: an obvious conundrum for ventures like SmartCells (SmartCells, 2016).

SmartCells spent the remainder of 2003 and most of 2004, while Dr. Zion was completing his Ph.D. thesis, developing a business model that could overcome the barriers of traditional VC financing. The team first developed their plan with the help of the M.I.T. Venture Mentoring Service (VMS), an organization comprising experienced technical entrepreneurs who assist aspiring entrepreneurs from the M.I.T. community (students, staff, faculty and alumni) in starting a business (MIT Venture Mentoring Service, 2015).

The co-founders gained access to major pharmaceutical companies through M.I.T.’s Industrial Liaison Program (ILP) and the pharmaceutical companies’ own scouting efforts in response to the publicity from the M.I.T. Entrepreneurship Competition. Through the early meetings with the pharmaceutical companies, SmartCells learned that pharmaceutical companies would not invest in SmartCells’ technology, no matter the potential, at such an early stage of product development. Particularly, pharmaceutical companies that had experience with insulin development would not invest until they saw a certain amount of additional risk reduction (e.g. safety assessment, manufacturability analysis, additional data from animal studies, etc.).

Given the pharmaceutical company interest in SmartCells’ technology and an early sense of the critical commercial risks, SmartCells attempted to develop a business plan that would fund the company sufficiently to address these risks and enable a high value pharmaceutical partnership. To that end, SmartCells decided to target angel investors to fund their company, and with the help of VMS, they found a number of

interested lead investors. The angel investors were drawn to SmartCells' high-risk, high-reward business strategy which allowed SmartCells to focus on a single product and address the key pre-clinical and early clinical technical risks in order to seek a potential partner as soon as possible.

Exit Strategy

With a relatively clear view of the exit, SmartCells worked backwards to develop a financing and operating plan that would enable significant returns on investment for the financial investors as well as the founders and employees (SmartCells, 2016). The team leveraged its discussions with VMS, pharmaceutical companies, early investors, and scientific medical advisors to delineate specific value-creating milestones. The crux of the plan (described in more detail in the Technical section) rested on the belief that, due to the nature of its glucose-responsive insulin construct, the company needed to demonstrate acute safety and performance in humans before obtaining a high value pharmaceutical partnership. Insulin activity and glucose-responsiveness can be readily assessed in animals and patients using standard protocols over the course of weeks, not years (Hovelmann, 2015). In addition, there is a more reliable correlation between insulin activity between humans and animal models than exists for most other pharmaceutical agents and disease areas (Al-awar et al., 2016; King, 2012). Furthermore, if a clinical study was required, SmartCells' first human clinical study would be able to determine the dose-dependent insulin activity as a function of patient blood sugar levels – the core benefit of the underlying technology - with relatively few patients over a short period of time (SmartCells, 2016). Therefore, the SmartCells team decided to raise

enough money to develop the best formulation, establish the product safety and efficacy in animals, and, if necessary, perform a clinical study to show glucose-responsive glycemic control in humans, while seeking opportunities to partner the project along the way (SmartCells, 2016). SmartCells' operations were therefore entirely focused on the pre-clinical and early-stage clinical development of SmartInsulin.

Mission Statement

SmartCells set forth the company's mission to become the first to deliver a self-regulating insulin injection for the treatment of diabetes. Diabetes continues to be a global pandemic, affecting over 415 million people worldwide according to the International Diabetes Federation, consuming an estimated 12% of global healthcare in 2015 (International Diabetes Federation, 2017). The American Diabetes Association estimated that in 2012 over twenty-nine million Americans suffered from diabetes (American Diabetes Association, 2017). Conventional insulin is rarely capable of normalizing patient blood sugar levels mainly due to its inherent risk of inducing life-threatening hypoglycemia if dosed inappropriately (Cryer, 2008). Inadequate blood sugar control then leads to the costly, debilitating sequelae of diabetes which include nerve damage, blindness, kidney disease, and cardiovascular disease (American Diabetes Association, 2002). SmartCells' aimed to address this unmet need by building the ability to sense and respond to blood sugar directly into the insulin formulation thereby allowing it to turn itself on when needed and off again when blood sugar levels normalized. If successful, SmartCells' technology would help increase patients' quality of life, enable

physicians to safely treat diabetes more aggressively, and increased third-party payers' annual savings from a reduction in their clients' healthcare costs (SmartCells, 2016).

To accomplish their mission, SmartCells needed to complete Investigational New Drug (IND)-enabling pre-clinical safety and efficacy studies using SmartInsulin and develop good manufacturing practices (GMP) to produce compliant SmartInsulin materials. Accomplishing these milestones would allow SmartCells to submit an IND application to the FDA for SmartInsulin to complete human proof-of-principle (Phase I clinical trials) (Van Norman, 2016). They could then establish a strategic partnership with a pharmaceutical company to support Phase II/III trials and regulatory clearance to introduce SmartInsulin for commercial use.

Operations

SmartCells' headquarters and operations were based in sub-leased space from Inotek Pharmaceuticals Corporation in suburban Beverly, Massachusetts (Frechette, 2013). The shared space provided laboratory equipment and an animal facility. Any additional essential equipment needed for a specific operation which was not available through the shared space agreement with Inotek was purchased in a previously owned or refurbished state (SmartCells, 2016). The in-house equipment allowed SmartCells to efficiently synthesize variants of the chemical entities that make up SmartInsulin and subject them to a broad range of specialized analytic tests. Eventually, Inotek outgrew the premises and had to sell off their equipment while SmartCells was in a position to grow. SmartCells assumed Inotek's lease at a significant reduction for 20,000 square feet

of lab and office space and was able to buy all of their equipment and animal facility resources for pennies on the dollar (SmartCells, 2016).

SmartCells was able to develop their own good laboratory practice (GLP) space with the newly acquired facilities. The expanded animal facility allowed for the housing and testing of a significantly larger numbers of rodents that were needed to conduct the requisite studies. The animal studies included the ability to induce, treat and monitor a large numbers of streptozotocin (STZ)-diabetic rats over long periods of time. Hyperglycemic clamp tests were performed on normal and STZ-diabetic rats for periods of up to twelve hours. Additionally, multi-day tests of insulin formulations were conducted while using continuous glucose monitors to record the results over the duration of the tests (SmartCells, 2016).

The additional space enabled the in-house production of GMP-material and support of out-sourced safety and efficacy testing of new insulin formulations by contract research organizations (CROs) on various animal models including normal and diabetic rats and pigs as well as dogs and cats. Furthermore, SmartCells utilized its own resources in conjunction with outside contractors to validate analytical and functional assays for use in manufacturing SmartInsulin materials. The choice of sharing space with Inotek proved to be one of the best decisions SmartCells made (SmartCells, 2016), allowing the company to deploy minimal amounts of cash to accomplish their goals even as the company prepared for clinical trials.

Financing

Angel Investment vs. Traditional Venture Capital

As described above, SmartCells was forced to look for alternative sources of financing as life-science VCs were moving away from "seed" financing of high risk, early-stage ventures. However, the team sought alternative financing for other, more practical reasons. Specifically, several VC partners who were interested in investing in SmartCells personally advised the founding team to avoid VC funding so that the team could retain significant control over the company and its direction, thereby participating in a greater portion of the upside (SmartCells, 2016). The belief was that a small, ambitious, creative and nimble team with the right kind of downstream incentives would be a better recipe for success than an imported VC team of management and board of directors without much "skin in the game" (SmartCells, 2016).

The SmartCells team, therefore, looked to angel investors for equity financing. Angel investors in 2003-2004 had been very active in information technology (IT), web-based, and device-oriented start-ups, but had comparatively little experience with pharmaceutical ventures (Balakrishnan, 2015; Partners in BioPharma Consulting, 2014; SmartCells, 2016). Furthermore, they had only limited amounts of capital available and were justifiably concerned that the company would eventually need more capital than they could provide, leading to a VC round which would inevitably overwhelm their interests in the company through dilution and preemptive rights. The significant financial resources needed to overcome the large technical and regulatory hurdles were virtually

the same whether SmartCells chose to pursue angel or VC investments. Therefore, the company had to develop an operating and financing plan that relied not only on angel financing and "sweat equity" from the founding management team, but also significant funding from non-dilutive government grant and charitable resources (SmartCells, 2016). The three financial pillars of angel financing, non-dilutive financing, and upside incentives for the team's hard work, had to be established and maintained such that the company's future success was dependent on each aspect.

Angel Funding

Raising $10M from angel investors was a key part of SmartCells success. Most of the money came in relatively small amounts, $25K to $50K, which necessitated a large investor base (SmartCells, 2016). In fact, SmartCells had around 150 individual investors by the time the company was sold (Booth, 2011). This created tremendous pressure on investor relations for an already small and taxed management team. However, the SmartCells team recognized this trade-off, and developed a plan through which board members and observers frequently communicated critical information to their constituents and distilled their responses to provide clear feedback to the SmartCells management team (SmartCells, 2016). After all, the terms on which the investors put up their money left a good upside to management if they were successful. These favorable terms incentivized SmartCells to be the best possible stewards of their investors' money, so that their rewards and the investors' rewards were well aligned. Example terms that were more favorable than typical VC terms included but were not limited to: minimally intrusive board representation, simple weighted-average anti-dilution, few restrictions on

future “up round” financing events, limited liquidation preference, higher valuations, and reasonable but not overly taxing information rights (SmartCells, 2016).

Despite the upside associated with angel investors, in general they can be more difficult than VCs due to their high expectations for very quick exits (less than three years) (SmartCells, 2016). When in reality, life-science startups require four to seven years to even select a drug candidate (see Figure 1). Additionally, angel investors, unlike their VC counterparts, may not have as “deep of pockets” so that if additional financing were needed, or if the next round of capital requirements were too large, the current angel investors would not have the means to help (SmartCells, 2016). The pros and cons associated with angel funding versus VC funding, compiled and organized from interviews with SmartCells team members and a review of the financing market, are presented in Table 1. Many of the investors in Series A, see Figure 1, continued to invest their pro rata shares throughout the company’s history; in some cases, the investors invested considerably more than their pro ratas in Series B, C, and D. That type of strong support was important for SmartCells. The angel investors believed in and trusted the management team, especially the CEO, to make good decisions on their behalf (SmartCells, 2016). However, as shown in Figure 2, SmartCells had to raise, in its last year, almost as much as it had raised in the previous five years to support the early stage clinical studies. The company had reached the limit of its ability to fund operations using its lean, capital-efficient model.

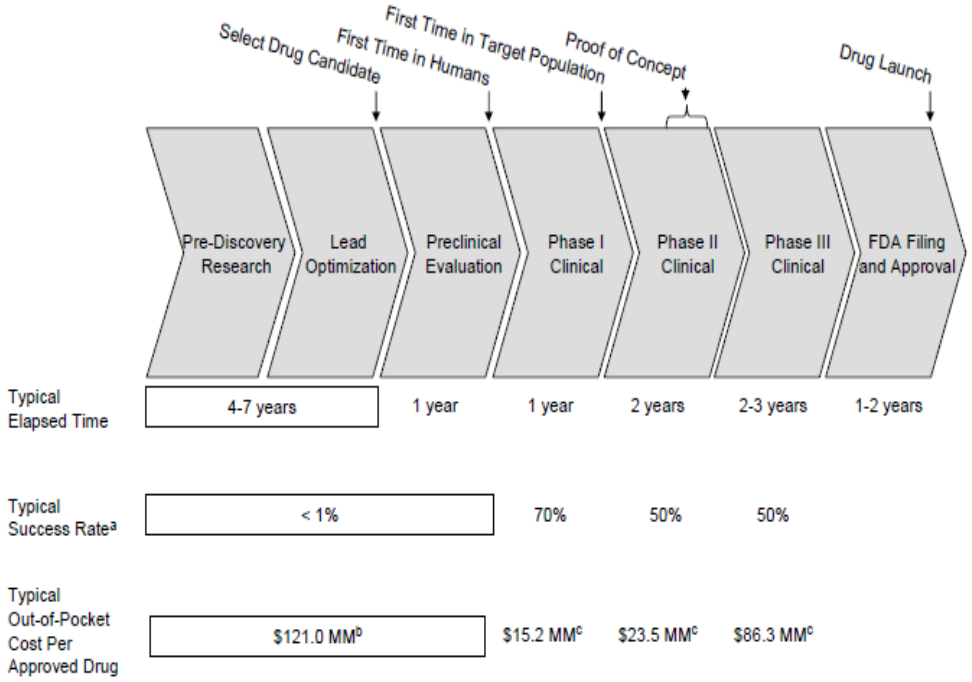

Figure 1. Typical new drug development approval process data from the FDA. Out-of-pocket cost significantly increase as clinical phrases progress. Additionally, SmartCells had less than a 1% chance of success (Huckman & Strick, 2010).

Table 1: Entrepreneurs' Perspective on Angel Funding vs. Venture Capital. The table represents the generally accept pros and cons of angel funding vs. VC funding from an entrepreneur's perspective.

	Pro	Con
Angel Funding	• Exit in 3-5 years • Exit with less than $5-10M invested capital • Potential for 10x return • Easily understood story • Group has personal connection to CEO • Financial investment from management team • Accepts relatively high pre-money valuations • Less governance and oversight • Vast network of high net worth individuals	• Less capital available • Time consuming • No safety net for founders and management team • Looking for exits around every corner • Less capital available • Time consuming • Less optionality if need to pivot
Venture Capital	• Large amounts of money • Long-time horizon 5-10 years • Provides management experience • Business connections	• Loss of control • Management control • Long and complex process

Acquisition of Non-Dilutive Funding

SmartCells received $30K in proceeds as the Robert P. Goldberg Grand Prize winner in the M.I.T. $50K Entrepreneurship Competition in May 2003. Subsequently, the company received its first outside financing through the sale of equity to private investors in September 2004. That month SmartCells also received notice of their first grant award from the National Institute of Health (NIH). The NIH and the National Institute of Diabetes and Kidney Diseases (NIDDK) both support the Small Business

Innovation Research programs (SBIR) which is a U.S. congress mandated program that helps fund small businesses to reach their commercialization aspirations (National Institutes of Health, 2017). The NIH/NIDDK SBIR programs would prove a robust and important pipeline of non-dilutive funding for SmartCells. A list of the NIH/NIDDK SBIR grants awarded to SmartCells with their issuance date and monetary allotment is presented in Table 2.

SmartCells worked very closely with their program officer and key personnel at the NIDDK so that they knew the status of the SmartCells' program along the way. SmartCells presented data to them on a regular basis in person and asked for their recommendations with respect to experiments and scope of Research and Development (R&D) activities (SmartCells, 2016).

National Institutes of Health. NIH grants were critical to SmartCells' success by providing a key source of non-dilutive funding that allowed them to cautiously use investor dollars for those items not reimbursable against grants, such as legal and administrative items. SmartCells' first grant was a special funding Phase 1 SBIR for $500K per year for two years. Typical Phase 1 SBIR grants awarded at that time were approximately $100K for one year (National Academies of Sciences & Medicine, 2015). The initial grant allowed SmartCells to start up the company's operations while the management team was concurrently raising their first $500K of financing. This led SmartCells to raise another $700K very quickly. The two Phase 2 SBIRs ($3M each) that SmartCells was awarded later were critical toward covering the expensive safety and manufacturing work required to test a product in the clinic. Without these grants awarded by the NIH, SmartCells would have had to privately raise the money from VCs,

suffer tremendous dilution, and lose the value of a flexible, knowledgeable management team.

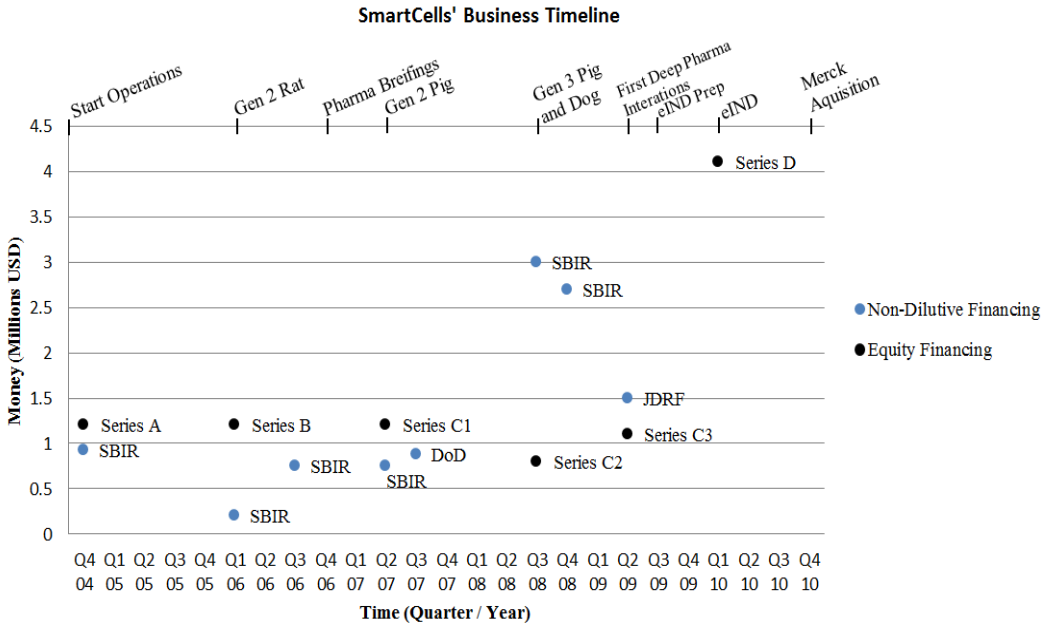

Figure 2. "SmartCells on one slide." SmartCells' product, business development and sources of financing over time.

Other sources of non-dilutive funding included a Research, Development and Commercialization Agreement, that concluded in August 2008, with the Juvenile Diabetes Research Foundation (JDRF) to support SmartInsulin development. This partnership brought in $1.5M to support risk-reducing animal studies aimed at understanding the difference in product performance among various mammalian species. Additionally, SmartCells was awarded a U.S. Army Peer Reviewed Medical Research

Program (PRMRP) grant for SmartInsulin large animal (mini-pig) safety and efficacy studies in August 2007. The Department of Defense grant brought in $850K.

Table 2: NIH/NIDDK SBIR grants. List of grants awarded to SmartCells from the NIH and NIDDK in the form of SBIR grants showing number, title, start date and amount of the grant.

Number	Title	Start	Amount
DK69870-01	Glucose-responsive, Self-regulated Insulin Delivery	Oct. 2004	$482,276
		Sep. 2005	$438,290
DK72774-01	RNA-Biopolymer Nanostructures for Smart Insulin Delivery	Aug. 2005	$195,241
DK69870-03	Safety Profile Optimization of Glucose-Regulated Insulin Formulations	Jul. 2006	$749,991
DK077292-01	Multimeric RNA Aptamers for Glucose-Responsive Insulin Formulations	Apr. 2007	$394,363
		Apr. 2008	$335,073
DK079482-01	SmartInsulin Stability, Process Development, Assay Validation and GMP Manufacturing	Aug. 2007	$283,515
DK080565-01	SmartInsulin ADME and IND-enabling Pre-clinical Studies	Mar. 2008	$1,116,164
DK079482-02	SmartInsulin Stability, Process Development, Assay Validation and GMP Manufacturing	Aug. 2008	$1,546,698
DK079482-03	SmartInsulin Stability, Process Development, Assay Validation and GMP Manufacturing	Aug. 2009	$850,859

Dilutive vs. Non-Dilutive Funding

SmartCells raised about $10M in dilutive equity financing (Series A, B, C and D) and about $13M in non-dilutive grants. The large contribution of grant money helped offset the technical risks and enabled SmartCells to raise more money at favorable valuations along the way. The grants not only helped the company to hone their R&D plan, but they also provided a key point of scientific due diligence for their investors. Importantly, when SmartCells needed to scale back operations to retool the new insulin formulation (see Technical section), they were able to leverage grant money to sustain them in the meantime, thereby avoiding the need to raise money at a time when the company was in technical or financial trouble. Furthermore, having grant money at the time of the financial crisis in 2008-2009 also allowed SmartCells to avoid having to raise money until after the markets recovered in 2010.

Obtaining grants also facilitated the sale of equity. Raising money from angel investors versus VCs allowed the SmartCells' management team to focus on the company's strategy without the need to defer to business models or technical decisions that may have been guided by a VC-backed board of directors. In general, the equity and grant funding kept pace with each other (see Figure 3). Another added benefit of combining the two modes of financing was that the equity financing could cover specific R&D activities during the time periods between each grant to offset the uncertainty in timing between receipt of successive grant funds. Quite frankly, neither vehicle alone was sufficient for SmartCells, but the combination was very effective.

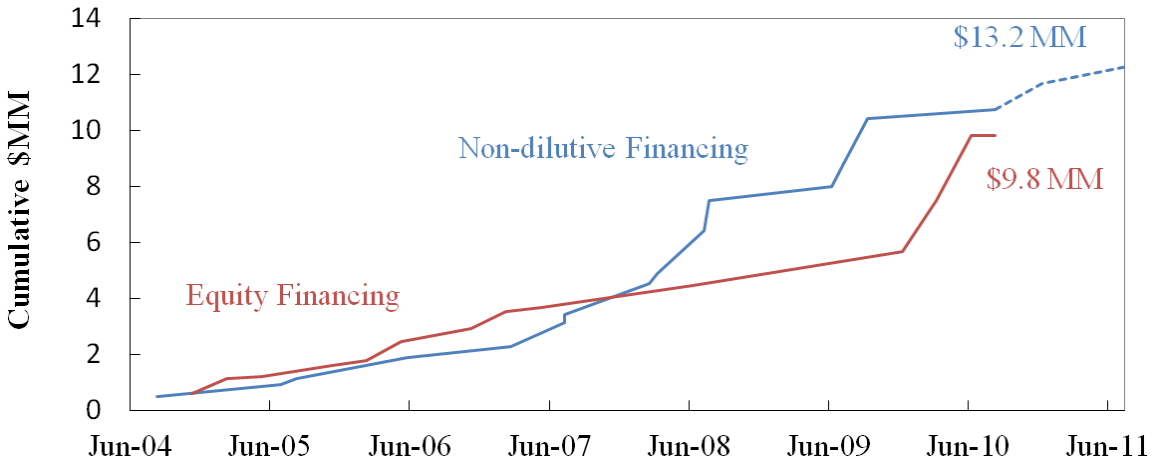

Figure 3: Equity vs. non-dilutive financing over time. The amount of capital SmartCells raised was relatively even between equity and non-dilutive financing throughout its lifespan. The dotted blue line represents a $3M grant SmartCells had to return to the JDRF due to the acquisition with Merck. This grant money would have helped fund the clinical trial.

Equity vs. Cash Compensation for Employees and Services

Everyone on the SmartCells founding management team valued their equity more than cash compensation, which served as a strong motivating force (SmartCells, 2016). The team paid themselves as much as was necessary to ease the burdens of home life so that they were minimally distracted at work. Having just enough funding to execute on their operating plan, SmartCells was never awash in cash like many VC-backed biotech start-ups. This kept their salaries down, and forced them to make critical decisions based on the fact that they needed to keep demonstrating product-related risk reduction and value. Their salaries were below the market value of VC-backed biotech start-ups; this policy helped align management expectations with those of the money-shareholders (SmartCells, 2016). Having a relatively small rate of expenditure contributed to a

mutually beneficial relationship as SmartCells was not overburdened with excessive management salaries, and was able to maintain a lean corporate structure. Many of the SmartCells employees, however, did not share their management's views despite the management team's attempts to explain the relative value. SmartCells management believed this difference had to do with either their lack of start-up experience or their being involved in start-ups whose equity never amounted to anything (SmartCells, 2016). This made it very difficult to find and retain the right kind of employees. SmartCells had seventeen employees when Merck bought it (the largest number in its history). Yet, the company had over forty-five people pass through its payroll over the years. Despite the employees' lack of confidence in the value of their SmartCells' equity stakes, most employees made at least four years their salary in a lump sum including bonus payments, stock option payments, and severance after the Merck acquisition (SmartCells, 2016).

Technical

The SmartInsulin development path relied on a combination of technical know-how, data-driven decision-making, hard work and serendipity. In fact, there were at least three critical moments during the six year development timeline that represented roadblocks to product performance and also presented opportunities to develop better, more robust embodiments of the technology.

Safety and Subcutaneous Efficacy

The technology licensed from M.I.T. consisted of a glucose-binding molecule (GBM) which reversibly crosslinked a glucose-containing polymer to which insulin was covalently attached. An illustration of the construct is shown in Figure 4. The materials were hydrogels that demonstrated adjustable glucose-sensitivity in the physiological range and long-acting, glucose-responsive blood glucose control in diabetic rats following an intraperitoneal (i.p.) implantation. Technical challenges posed included: development of a hydrogel that could be injected subcutaneously (s.c.) through a standard insulin syringe; a GBM that was safe for human use; and a polymer that would allow insulin s.c. absorption into the circulation system after a glucose challenge. None of these technical challenges were particularly easy. Most notably, the GBM from M.I.T. was based on the plant lectin, Concanavalin A (Con A), which was known to be immunogenic and mitogenic in mammals. Furthermore, the dextran polymer was too big to pass through the s.c. barrier, but smaller polymers were not capable of crosslinking to form the hydrogel (Zion, 2004).

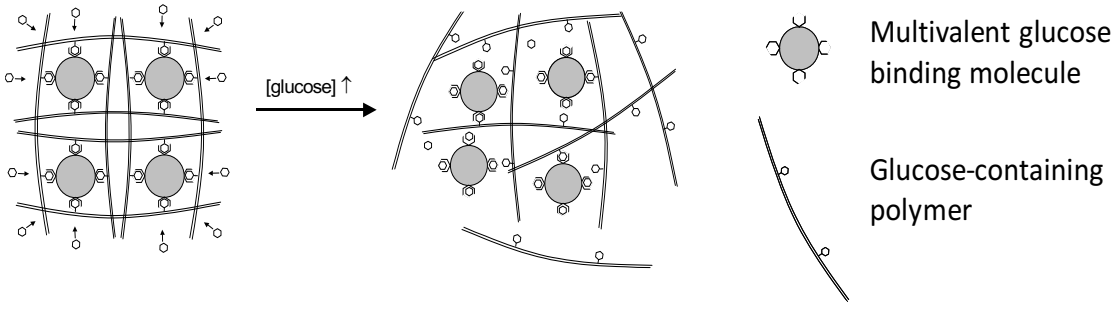

Figure 4: Illustration of Con A and a glucose containing polymer interaction. Physiological free glucose displaces the glucose polymer to disrupt the Con A network.

After approximately two years, the SmartCells team had developed a way to chemically modify the Con A to minimize its adverse safety issues. They had also developed a glucose-containing polymer that was still large enough to form hydrogels but would break down through the action of enzymes into smaller components that could be absorbed from the s.c. layer after it was released in response to glucose. The combined system could be injected s.c. through a syringe, and the resulting materials demonstrated superior glucose control in diabetic rats (SmartCells, 2016).

Dealing with Disparity in Performance between Rodents and Large Animals

Rodents are far from ideal models of human diabetes for many reasons, including their notorious resistance to the effects of insulin as well as the increased speed with which compounds can absorb from the s.c. layer. Therefore, SmartCells obtained grant and equity financing in late 2006/early 2007, as shown in Figure 2, to evaluate their materials' performance in the more translatable pig model. A set-back was identified when the materials that worked perfectly well in the rodents caused massive hypoglycemia in pigs. The source of the disparity was tracked down to differences between the rodents' and pigs' enzyme activity. The enzymes that broke down the glucose-containing insulin polymer to enable s.c. absorption were "so much more active in pigs" (SmartCells, 2016). The polymer was digested even before it was released by glucose from the hydrogel. In essence, the feature that enabled s.c. performance in rats became a serious liability when it came to pigs. Further in vitro studies demonstrated differences in enzyme activity across multiple species, including humans. Therefore, the polymer degradability had to be tuned properly for each species of interest. Given that

the FDA requires evaluation in a rodent and non-rodent animal model prior to testing in humans, the SmartCells team was faced with the daunting task of designing a system that i) was safe and effective in the two evaluation species despite species differences in enzyme activity and ii) had a reasonable chance of working in humans. In the face of challenge, the SmartCells management team opted to forgo the enzyme-degradable system and design a new system that could still form hydrogels using glucose-containing molecules that were small enough to absorb from the s.c. layer. In order to provide enough funding to accomplish this goal the company had to slash its workforce from twelve full-time employees down to five, put the CEO and CSO, Drs. Zion and Lancaster, respectively, back in the lab full-time, and require everyone to work six to seven days per week for more than fourteen hours per day. This represented a major turning point in SmartCells' history. Many stakeholders look back at this as a "bump in the road," but the management team knew the gravity of the situation and responded accordingly (SmartCells, 2016).

New Sugar Chemistry and Serendipity

After approximately nine months, the team emerged having developed specially designed, branched sugars that when conjugated to insulin could form hydrogels, but could also absorb quickly into circulation when released by glucose without requiring enzyme degradation. SmartCells then rebuilt its GBM technology to be compatible with the newly designed sugar chemistry. In late 2008, the company restarted discussions with potential partners offering up the new technology for consideration. In addition, the company started recruiting additional employees to increase product development efforts.

During that time, Drs. Lancaster and Zion noticed deviations with the newer insulin-sugar conjugates that warranted further attention. It appeared that some embodiments could perform in a glucose-responsive manner even without forming hydrogels with the GBM. After extensive investigation, the team discovered that there were certain GBMs (lectins) already present within the body that could bind and render inactive the insulin conjugates but release the materials at higher sugar concentrations. This rather serendipitous discovery would render the exogenous GBM unnecessary and greatly simplify the safety, manufacturing, cost, and delivery of SmartInsulin. Even though it was still risky to abandon the GBM, the SmartCells team decided to completely focus on this new discovery. Furthermore, it was very difficult for the SmartCells management team to explain to the potential pharmaceutical partners that the product they were evaluating had been abandoned in favor of a newer but less proven embodiment. Nevertheless, the team understood that this was the right move in the long run, and several of the big pharmaceutical companies, including Merck, decided to continue their due diligence and pursue a potential development partnership. In fact, the new embodiment proved to be so appealing that Merck offered to acquire the technology in 2009 based solely on the rodent data. Nevertheless, in mid-2009 another major turning point materialized (SmartCells, 2016).

Lack of Translation (the Sequel) and Final Push

After the newest generation of the technology was proven in rodents, the team pushed aggressively toward pig studies. Once again, however, the materials that performed well in rodents failed to translate to the higher-order mammals. But in this

case, the team had identified a material that worked well in pigs and linked the lack of translatability to differences in insulin sensitivity. These results came when Merck was ready to close an acquisition deal. SmartCells made the ethical decision to disclose the lack of animal translatability to Merck which caused them to walk away leaving SmartCells and the deal in limbo. Although the SmartCells team felt more confident about the commercial prospects of the technology, they needed to make sure that they chose the sugar chemistry that would best enable a human product. Concerned that no animal model would tell the whole story, the team decided to design and raise money to perform a first-in-man clinical study. From late 2009 to early 2010, the company raised almost as much money as they had over the previous five years ($4M+) to build out its own GMP manufacturing, quality control, and GLP assay laboratory; to prepare clinical grade material; to obtain regulatory approval for the exploratory clinical study; and to initiate the study. Concurrently, the team applied for and received a $3M grant to support the clinical studies. SmartCells was now ready to demonstrate that its materials could perform as advertised in humans. However, the team made one last push to see if any pharmaceutical company was interested in partnering before they obtained the dispositive clinical data. Merck and one other company decided that SmartCells' technology was attractive enough to want to take over the program. Paradoxically, the pending clinical study was a strong incentive to close a deal as soon as possible. Both companies wanted to make sure that they could own and develop the technology as they saw fit and did not want SmartCells "rushing" into clinical studies to prove a point. SmartCells steadfastly adhered to their November 2010 deadline to initiate clinical trials, and Merck was forced to move with a closeout bid (SmartCells, 2016).

The work of SmartCells to reach this point in the development of SmartInsulin resulted in over of twenty utility and/or design patents issued from the United States Patent and Trademark Office (USPTO). The list of patents held by SmartCells is presented in Table 3.

Table 3: SmartCells' Patents. The development of SmartInsulin resulted in over twenty patents from the USPTO.

Title of Patent	Publication Number
Binding Site Modified Lectins and Uses Thereof	US 20140342980
Conjugate Based Systems for Controlled Insulin Delivery	US 20140274888
Uses of Macrophage Mannose Receptor to Screen Compounds and Uses of These Compounds	US 20130302825
Drug-Ligand Conjugates, Synthesis Thereof, and Intermediates Thereto	US 20130131310
Recombinant Lectins, Binding-Site Modified Lectins and Uses Thereof	US 9068013
Recombinantly Expressed Insulin Polypeptides and Uses Thereof	US 9074015
Drug-Ligand Conjugates, Synthesis Thereof, and Intermediates Thereto	US 20130190475
Polymer-Drug Conjugates	US 20120135919
Synthetic conjugates and uses thereof	US 8940690
Drug-ligand conjugates, synthesis thereof, and intermediates thereto	US 8933207
Crystalline insulin-conjugates	US 8906850
Exogenously triggered controlled release materials and uses thereof	US 8846103
Methods for reducing the mitogenicity of lectin compositions	US 8729242
Method for controllably releasing a drug conjugate within subcutaneous tissue in response to the local concentration of an indicator	US 8697643
Terminally-functionalized conjugates and uses thereof	US 8623345
Polynucleotide aptamer-based cross-linked materials and uses thereof	US 8603529
Soluble non-depot insulin conjugates and uses thereof	US 8569231
Stimuli-Responsive Systems for Controlled Drug Delivery	US 8357400
Stimuli-Responsive Systems for Controlled Drug Delivery	US 8062668
Methods for Reducing the Mitogenicity of Lectin Compositions	US 7687608
Stimuli-Responsive Systems for Controlled Drug Delivery	US 7531191

Human Capital

Another key attribute that contributed to SmartCells' success was their personnel. Team-building and human resource management are crucial to the success of any enterprise, but are more acutely critical to the success or failure of a start-up company. There is nowhere to hide in a start-up, and there is not enough time or money to suffer ineptitude or misalignment of work ethics. In the early days, SmartCells was so cash-constrained that everyone was wearing multiple hats to complete the work. But as SmartCells continued to de-risk the R&D program, they could raise more and more money allowing them to make additional hires (SmartCells, 2016).

Founding Management

Dr. Zion, co-founder, CEO and president, was able to define and articulate the grand vision and tie all of the different company aspects (e.g. financing, investor relations, technical development, grant writing, public presentations, etc.) into one basis on which to make critical decisions. Dr. Zion understood both the technical and business risks associated with bringing a start-up pharmaceutical company through to fruition. In the early days of SmartCells, this helped tremendously, especially when fundraising. Prospective investors could "one-stop shop" for answers to their questions (SmartCells, 2016).

Dr. Lancaster, co-founder and Vice President of Research and Development, brought a sharp experimental mind with attention to scientific rigor. He was able to

concentrate more on the science and technical aspects without having to immerse himself in the corporate governance. He led the in-house R&D team that had rapidly developed and tested SmartInsulin formulations with a variety of performance profiles. He was eager to learn as much as possible from the experimental failures (SmartCells, 2016).

Mr. Herriman, co-founder and Vice President of Operations, brought hands-on start-up experience and a more seasoned perspective on the fundamentals of building and running a company. He was able to focus on company finances, investor relations and daily operations without having to dig too deep into the science (SmartCells, 2016).

The management team members were aware of each other's primary sphere of responsibility and willing to step in to help as needed. SmartCells had a small, functional and focused management team who embodied the entrepreneurial spirit. The co-founders of Zion, Lancaster and Herriman each possessed different complementary skill sets that worked well together. This was especially important in the beginning as SmartCells could only afford a handful of employees. The founding members were intellectually honest and focused on commercial success and were not afraid to ask for help when they needed it. They were results-oriented and had an informal rule of "no office politics" (SmartCells, 2016). This produced straightforward, frank and honest communication with success being based on investor return and not on raising capital or capturing headlines. They had no pre-conceived notions about the outcomes of experiments, what the final product had to look like, or whether to run the company as a virtual company or perform everything in-house. They were very open-minded and let the experimental data guide their decision making. It should be noted that it is unusual for a founding

management team to stay intact throughout the entire life of the company (SmartCells, 2016). It is a testament to the quality of the team and its contribution to success.

Key Employees

As cohesive as the founding group was, they had little experience with hiring and firing employees, and as such, started hiring employees with a cautious optimism. It was after just the first nine months that the founding management team realized that they would have to make hard decisions and start to fire team members who were not pulling their own weight. Those who came to the company feeling entitled did not last very long.

Subsequent employees were successful if they brought with them the idea that hard work and sacrifice up front could lead to outsized rewards in the long run. Employees that were most willing to work very hard, show initiative in the lab, and adapt to the ever-changing needs of the R&D organization held the most important qualities SmartCells was looking for. SmartCells found that there was no easy way to screen for these employees in the interviewing process so they just had to "hire these applicants and try them out to see if they had the hands-on, hard-work ethic, and flexibility required to mesh with SmartCells' needs" (SmartCells, 2016).

The optimism turned to cynicism, though, as most employees disagreed with the risk-reward proposition as discussed in the Financial section. Perhaps it was the management team's lack of experience in hiring or their unrealistically high expectations, but regardless of the cause, finding and retaining high quality employees was the bane of

SmartCells' existence. However, the rapport among Drs. Zion, Lancaster and Herriman kept the company going through these ups and downs (SmartCells, 2016).

After the team downsized in 2007-2008 to develop its next generation technology, management was committed to rebuilding the team using the lessons they had learned over their previous four years. As was the case on many occasions, a little luck was involved. The company from whom SmartCells had been subleasing space had to downsize dramatically at the same time SmartCells was looking to grow. Having developed collaborative working relationships already with key employees from the landlord company, it was easy to hire them after they were laid off. In addition, research groups at M.I.T. and Harvard were specifically targeted to find high functioning, ambitious, newly minted Ph.D. graduates. SmartCells offered to pay these new recruits higher than market value to make it worth their while. Lastly, SmartCells found key employees who were caught in the economic downturn of 2009 who may have otherwise been unavailable to a small cash-strapped start-up company. SmartCells did retain some key hires before the downsizing who performed the day-to-day work with the animal studies. The animal study work was critically important to the company's success (SmartCells, 2016).

As mentioned above, there were seventeen employees at SmartCells when the company was sold to Merck in 2010, the most the company had ever employed at one time. Based on interviews with key SmartCells employees, there was a general consensus that the team was the most productive and high functioning of any past group; the best team was "left on the field" at the end (SmartCells, 2016).

Advisors and Board Members

In addition to the management team and key recruits, SmartCells had additional support and collaborators from M.I.T., Massachusetts General Hospital, Joslin Diabetes Center, JDRF, NIH, former biotech executives, and industry experts. Among these collaborators was Dr. Alan Watson, who served as Vice President of SmartCells Business Development. Dr. Watson was formerly the Chief Business Officer at Elixir Pharmaceuticals Incorporated and Senior Vice President of Corporate Development at Cubist Pharmaceuticals Incorporated (Akston Biosciences, 2017).

A few notable Scientific Board members included Dr. Jens Brange, who is one of the foremost experts on insulin pharmaceutical development, and Dr. S. Edwin Fineberg, the leading authority on measuring insulin antibodies. SmartCells Medical Advisory Board included Dr. Gordon Weir, Dr. Howard Wolpert, Dr. Enrico Cagliero and Dr. Lloyd Axelrod who are authorities on islet function, insulin pump development and clinical diabetes research (Bloomberg, 2017).

Chapter IV

Discussion

SmartCells was not your typical biotechnology company. It is truly remarkable that such a short-funded biotechnology company was able to reduce product risk to the point of achieving one of the largest pre-clinical life-science deals ever. Among the numerous elements throughout this paper that enabled SmartCells to be successful, there are three main points that aspiring entrepreneurs and investors need to understand before attempting to adopt the "SmartCells model": i) having access to non-dilutive capital, ii) a disease application for which the risk could be significantly reduced in pre-clinical studies or very early clinical studies, and iii) a team that is capable of shifting directions or reinventing itself. These areas are at the heart of this successful venture.

SmartCells' success did not evolve overnight. It took time to develop the right business model to take advantage of this opportunity. SmartCells adopted a method of success by raising relatively small amounts of money from angel investors and grants and deploying the capital in such a way that would create incremental value as they deployed each tranche of resources.

As the International Federation of Pharmaceutical Manufacturers Association (IFPMA) point out in their 2004 paper published on the World Health Organization's website, "Risk is a fundamental element in pharmaceutical R&D". The IFPMA paper

further established that bringing an idea to fruition is highly reliant on reducing the time and costs associated with regulatory approval (World Health Organization, 2004). With this in mind, SmartCells had to minimize the project's risk to the point that a large pharmaceutical company would partner with them or acquire the asset outright. The plan was by no means free of risk. For example, it was difficult to determine if and how much a pharmaceutical company would pay SmartCells before they could no longer resource the development efforts. It was for this reason that SmartCells had concrete engagement with possible pharmaceutical partners early on - so that they would know the companies' concerns and address them as soon as possible.

A company, at some point, needs to be able to obtain a term sheet from at least one pharmaceutical partner before the company tries to raise too many resources. A company can always reject a pharmaceutical partner's terms as being unfavorable and decide to move forward at-risk on its own, but a company that receives no term sheets before it mounts a clinical effort is destined to fail with the SmartCells business model. A lack of interest is likely to persist even after the company raises and spends a lot more money. Simply put, if there is no assurance that the company can achieve an exit after its planned clinical study, the company might be without a chance for a successful pharmaceutical deal.

SmartCells had deal terms from multiple pharmaceutical companies two years before it sold to Merck. The deal terms were not overly favorable, but having these terms in hand signaled to SmartCells that their biggest risk shifted from running out of money to having to settle for a less than optimal deal (SmartCells, 2016).

Angel Investors and Access to Non-Dilutive Funding

When SmartCells was raising money from angel investors, there was no integrated network for angel investors to share information regarding business opportunities (Sohl, 2004). The absence of this network could be because there were far fewer life-science angel investors present when SmartCells was raising money than there are today. This required SmartCells to go out and "tell the story" and engage in diligence many times over. Presently, information sharing and diligence is more syndicated among the angel investors. This means that if one group likes a deal, a company is likely to get a lot more money flowing in passively from the other groups based on the recommendation. The opposite is also true – if a company makes a mistake with one group it may be difficult to gain traction with the others (SmartCells, 2016).

As stated earlier in the Finance section, SmartCells ended up having about 150 investors. Success does breed success as it was very difficult for SmartCells to raise money in the early days, but as they made progress and obtained additional grant funding, those investors and new investors decided to participate. This helped them expand the investor base and raise money more easily. The investment amount per investor varied from a few thousand dollars to about $1M (SmartCells, 2016). None of the investors contributed any significant expertise to the company and it was diffuse enough that they had little influence on the company. Companies relying on VC's investment risk VC's implementation of their own management as seen in Table 1. Having many individual investors rather than a few institutional ones gave the management team the ability to set the course for the company. A large pool of investors provides stability in that if some

investors did not continue to invest there were always others. However, the large pool of individual investors did make it difficult to get the required signatures to approve the deal with Merck (SmartCells, 2016).

Grants played a major role in funding and, according to the SmartCells' management team, SmartCells would likely have failed without grant support. SmartCells raised almost $10M from angel investors, which is "pushing the limit of angel investing" (SmartCells, 2016), and required the same amount from grants to succeed. Raising $20M from just angel investors would have been close to impossible for SmartCells (SmartCells, 2016). Aside from the financial support, grants provided validation of the merit of the technology and approach. The grant processes are highly competitive, and the total amount of grant money is limited. By convincing agencies to continue granting money to SmartCells, it was possible to signal to investors, prospective investors and to prospective pharmaceutical partners that SmartCells had technology worth their investment. The process of writing grants, especially SBIRs, allows for the company to hone its message, periodically take stock of its technical progress, and critically analyze the next logical steps of risk reduction. Additionally, maintaining grants instills a strict culture of financial stewardship and accounting that translates through the rest of the facets of the company.

Although obtaining grant money is looked upon favorably, the downside is the timing and restriction on the use of funds. Grants typically do not pay for brick and mortar expenses (e.g. rent, lawyer costs, patent costs, equipment, administrative personnel, etc.) (National Science Foundation, 2017). Even for good applications, a company might have to wait up to a year after submission to receive initial funds due to

budgetary restrictions or programmatic prioritization issues. This makes it very difficult to plan and budget for activities. Additionally, grants aren't purely non-dilutive. The government has "march-in" rights to the IP if necessary. The government only intervenes in cases where "there is a threat to public safety", so it is a low, but not zero, risk (National Institutes of Health, 2013).

A major risk was that SmartCells' funding did not leave a lot of room for error. The reward, though, was the ability to hold on to a comparatively larger portion of the upside if they were successful than if they had raised more money from VCs in the beginning. This was one of the major achievements that may have been unknown or underappreciated about SmartCells - just how little of a financial safety net with which they operated while funding their operations.

Disease Application Risk Reduction

The cost of developing new drugs increases significantly as a possible therapy proceeds from pre-clinical to early clinical to late stage clinical studies, as shown in Figure 1. SmartCells had to raise almost as much money in its last year than in its previous five years just to mount one early stage clinical trial (Figure 2). SmartCells still needed a $3M grant from NIH to maintain stability. The next clinical trial would have cost upwards of $25M thereby rendering continued angel financing impossible (SmartCells, 2016). If an entrepreneur cannot show a concrete value proposition and risk reduction endpoint that can be practically achieved with just angel and grant money, there

is little reason to raise angel money in the first place. Treating diabetes and demonstrating improved glycemic control fits this category well, but this is not necessarily true for many other fields. One exception is the field of orphan diseases for which no therapy exists, where clinical trials generally involve small numbers, and the risk-reward equation is highly in favor of the new drug.

The diabetes space is unique in this aspect in that animal models are usually more predictive of what will happen in the clinic (Al-awar et al., 2016; King, 2012). Glucose control in diabetes is an example of a case where one may not be able to remove all of the risks of clinical success, but one can significantly decrease the risk by executing targeted studies in rodents, pigs and dogs. Furthermore, the timelines required to determine improved glycemic control are measured in days and weeks for acute control and just months for long term effects (HbA1c levels) (Saudek & Brick, 2009). Even more importantly, the link between HbA1c and long-term outcomes (e.g. retinopathy, neuropathy, nephropathy, and microvascular complications) has been established by the landmark studies of The Diabetes Control and Complications Trial (DCCT) and U.K. Prospective Diabetes Study (UKPDS). The DCCT and UKPDS studies have both convincingly demonstrated that better blood glucose control significantly reduces the development of complications in patients with diabetes. This established link is accepted by clinicians, pharmaceutical developers, and regulatory agencies as a meaningful biomarker for clinical benefits (American Diabetes Association, 2002).

In contrast, cancer, Alzheimer's disease, anti-infectives, and cardio-vascular disease are areas in which there is intense competition, lack of translation from pre-clinical models, little chance to prove efficacy with small clinical trials and requirements

for long, involved studies to determine the benefits to patients (Franco & Cedazo-Minguez, 2014; Mak, Evaniew, & Ghert, 2014). It would be very difficult to build a company in these areas using the "SmartCells model."

For non-technical stakeholders (e.g. certain investors and board members) it can be very difficult to accept the need to fundamentally change the underlying technology to make the ultimate product more likely to succeed in the future, as SmartCells had to do in 2008 when they retooled the formulation. The financial stakeholders' investment thesis relies, however naively, on the idea that they are betting on a technology and that the people advancing the technology are potentially replaceable, if necessary. However, the more experienced investor bets on the people who can shape the technology to achieve the best outcomes. Fortunately, SmartCells had enough people in the right places who held the latter to be true as opposed to the former. Such a mindset is critical for early-stage technology ventures.

Dynamic Leadership

One of the most important aspects of any venture is the team and management. This is especially true in that it takes a lot of time to build a team that can work well together in the high stress, high expectation and highly uncertain environment of a company like SmartCells. In other words, it takes time to develop a team that is capable of shifting directions or reinventing itself if the situation calls for it. VC-backed companies with more funding can afford to hire more people than are needed and can

perhaps better endure inefficiencies. Angel-backed companies may run out of time or money before they can build the right team. Fortuitously, SmartCells survived long enough to get to where they needed to be. Companies choosing to adopt the "SmartCells model" should not underestimate the human resource challenges presented by a minimally funded, high risk technology venture. Additionally, if the management team does not have the boldness to eliminate employees at the first signs of distress, then the "boot strap" financing model is not for them (SmartCells, 2016).

In 2007-2008 when the formulation needed to be rebooted, management had to reduce the number of employees from twelve employees to five in order to retool the technology while conserving capital. Subsequently, SmartCells was careful in bringing on staff as they had gone through the experience on having to downsize when they had some scientific setbacks. More people did not necessarily mean things went better or faster. Of the seventeen employees that worked for SmartCells at the time of the Merck acquisition, approximately ten were hired within the previous year. Almost all of them were involved in laboratory work as SmartCells increased productivity heading toward clinical trials. The best recruits came toward the end of SmartCells lifetime and were responsible for manufacturing, assay development, and basic mechanism of action studies. SmartCells needed to pay them at or above market salary to entice them to come aboard. At that time, SmartCells had raised enough money do so. It was only then that SmartCells was able to field a team that had no holes (SmartCells, 2016).

SmartCells developed multiple versions of its technology over the years due to critical failures with each successive version. Most teams do not have the insight or

courage to recognize the need for change, advocate for the change, and convince less flexible stakeholders of the need (SmartCells, 2016).

Some management teams are capable of making changes, but they surround themselves with stakeholders who either don't understand the need or are inherently resistant to radical changes. As discussed above, when raising money from a large number of individual investors, one increases the odds that any one vocally discontent stakeholder actively resists the necessary changes required to position the company for success. A new enterprise has to be careful to make sure investors understand just what they are getting into when they make their investments. A good management team needs to be headstrong in these instances and do what is ultimately ethically and legally right.

Teams that lack deep experience with and knowledge of the technology in their leadership are destined to fail with the "SmartCells model." The leaders will rely on technical employees, who may not be as committed, to recommend the right kind of directional changes (SmartCells, 2016). The leaders will not have a technically critical eye for figuring these things out on their own. This is unequivocally one of the key strengths of SmartCells. Not only did their management team have good business acumen, but they were scrupulous and reputable scientists who understood the underlying technology.

If an entrepreneur can find a pharmaceutical space that allows their venture to reduce technical risk early and a conscientious management team that religiously adheres to capital efficiency as described in this case study, then the "SmartCells model" will be advantageous.

Future of SmartInsulin

Merck has subsequently renamed SmartInsulin to MK-2640, and its lead candidate just completed a Phase 1 trial as this thesis is being drafted. Using healthy and diabetic participants, the trial gathered data on the safety and tolerability of intravenous doses while obtaining preliminary plasma pharmacokinetic profiles (Levy, 2015). The SmartCells management team has subsequently parlayed their success into another start-up venture named Akston Biosciences Corporation (Akston Biosciences, 2017).

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